American Journal of Medical Genetics 66:184–186 (1996)

De Novo Balanced Translocation (6;18)(q21;q21.3) in a Patient With Heterotaxia

Rumiko Kato, Yutaka Yamada, and Norio Niikawa

Department of Human Genetics, Nagasaki University School of Medicine, Nagasaki (R.K., N.N.), and Department of Pediatrics, Hakodate Chuoh Hospital, Hakodate (Y.Y.), Japan

We report on a sporadic case of heterotaxia with a de novo chromosome structural abnormality. The patient had inversely located heart (dextrocardia), stomach, duodenum, and cecum. In addition, she had cerebral atrophy, hypertelorism with telecanthus, infraorbital skin furrows, ear-lobe grooves, prominent maxilla and teeth, large carp mouth, short fifth fingers with limited flexion, generalized hypotonicity, and severe psychomotor retardation. High-resolution chromosome banding analysis demonstrated an apparently balanced translocation: 46,XX,t(6;18)(q21;q21.3). It is hypothesized that both heterotaxia and the chromosomal abnormality in the patient are causally related and a putative situs determining gene has been disrupted by the chromosome break, i.e., a position effect or a cryptic deletion at around the breakpoints. The translocation in our patient may be a good source for positional cloning of the gene.

KEY WORDS: heterotaxia, translocation, 6q21, 18q21.3, situs determining gene, Iv, Inv, connexin43 gene

INTRODUCTION

Heterotaxia, a lateralization defect occurring in an early embryonic period, is characterized by inverse position of visceral organs frequently associated with chest and abdominal malformations, such as tetralogy of Fallot, transposition of great vessels, pulmonary valve stenosis, ventricular/atrial septal defect (ASD), and asplenia-polysplenia. Heterotaxia occurs approximately in one in 10,000 births. Although it is generally accepted that lateralization, left-right asymmetry, of visceral organs is genetically determined, its mechanism has not been clarified. Several different inheritance modes have been proposed for familial heterotaxia: autosomal recessive [Arnold et al., 1983; Gatrad et al., 1984; Czeizel, 1987; Distefano et al., 1987; Zlotogora et al., 1987], autosomal dominant [Niikawa et al., 1983; Alonso et al., 1995], or X-linked recessive inheritance [Casey et al., 1993]. Different inheritance patterns suggest that multiple genes contribute to the determination of left-right asymmetry. Chromosome structural aberrations reported to be associated with heterotaxia may indicate the localization of the putative gene(s) for situs determination to the breakpoints: t(12;13)(q13.1;p13) [Wilson et al., 1991] and inv(11)(q13q25) [Fukushima et al., 1993]. Here we report another sporadic case of heterotaxia with a de novo balanced chromosome translocation.

CLINICAL REPORT

The female patient was born at 40 weeks of gestation with a birth weight of 3,090 g to non-consanguineous, phenotypically normal parents. The pregnancy and delivery are uneventful. At age 1 month, a pediatrician noted that her heart sounds were heard at the right fourth intercostal space and the liver was palpable 1 cm below the left costal margin. When seen by us at age 10 years, she weighed 22 kg (-2.0 SD) and measured 123 cm (-1.5 SD). She had generalized hypotonicity and severe psychomotor retardation; she could not stand up without support nor speak a word. Minor anomalies noted were as follows: hypertelorism with telecanthus, infraorbital skin furrows, ear-lobe grooves, prominent maxilla and teeth, large mouth (Fig. 1A), and short fifth fingers with limited flexion. A chest-abdominal roentgenogram showed dextrocardia and a gastric bubble in the right upper abdomen (Fig. 1B). Barium roentgenogram demonstrated a left stomach, reversely located duodenum and left cecum. Barium enema, scintigraphy, and catheter examinations were refused by the parents. Sleep records of electroencephalogram (EEG) were normal. Computerized tomography (CT) of the brain demonstrated cerebral atrophy. She had no history of recurrent infections suspected of splenic dysfunction. High-resolution chromosome banding analysis showed an apparently balanced translocation

Received for publication November 11, 1995; revision received February 14, 1996.

Address reprint requests to Dr. Rumiko Kato, Department of Human Genetics, Nagasaki University School of Medicine, Sakamoto 1-12-4, Nagasaki 852, Japan.

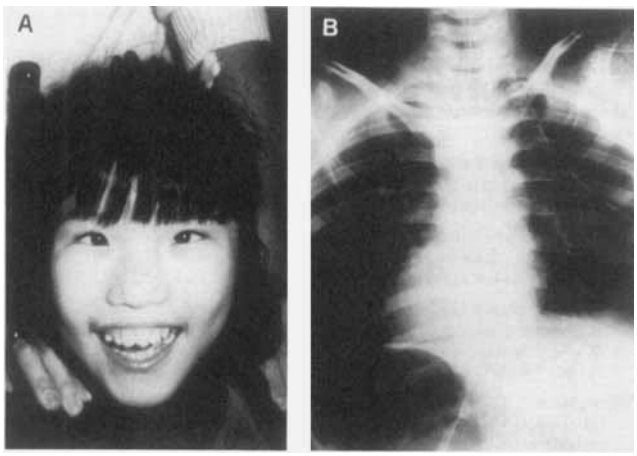

Fig. 1. Minor anomalies on the face (**A**), and dextrocardia and a gastric bubble in the right upper abdomen (**B**).

between 6q21 and 18q21.3 (Fig. 2). Karyotypes of her parents were normal. Thus, the karyotype of the patient was interpreted as 46,XX,t(6;18)(q21;q21.3) de novo.

DISCUSSION

The present case of heterotaxia was sporadic and her translocation a de novo type and balanced. It is a hypothesis that both the situs and chromosomal abnormalities are causally related and that a putative situs determining gene was disrupted by the break, i.e., a position effect or a cryptic deletion at around the breakpoints. Thus, the translocation in our patient may be a good source for positional cloning of the gene. Alternatively, in view of the presence of other phenotypic abnormalities, the chromosomal rearrangement was coincidental.

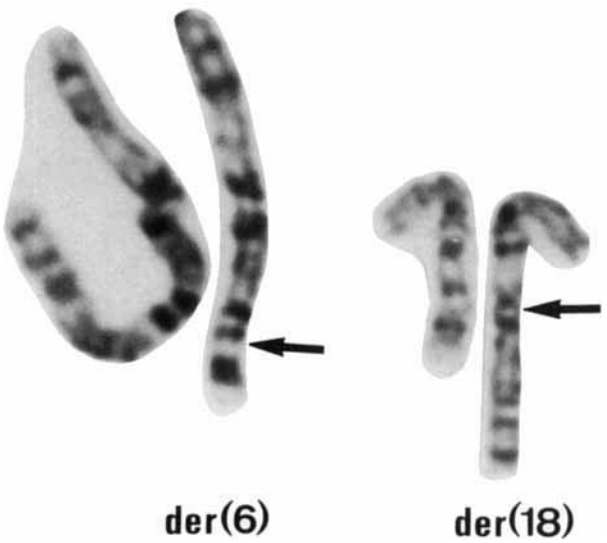

Fig. 2. Partial idiogram of the patient. Arrows show breakpoints.

To 6q21-q23.2 that is at or near one breakpoint in our patient, the human connexin43 gene (*GJA1*) was assigned [Corcos et al., 1993]. The gene product, connexin43, is one of the connexin proteins which make up the intercellular membrane channels of gap junctions. Recently, the connexin43-gene knock-out mouse was made [Reaume et al., 1995], and the null mutation of the gene resulted in neonatal death due to a swelling and blockage of the right ventricular outflow tract from the heart. The anomalies in this mutant mouse resemble congenital pulmonary stenosis in humans. In fact, *GJA1* mutations have been identified in 7 of 30 patients with a variety of congenital heart diseases, such as asplenia-polysplenia, atrial or bronchopulmonary isomerism, and familial ASD [Britz-Cunningham et al., 1993, 1995]. Although our patient had no obvious structural heart anomalies, it remains to be seen whether there is a *GJA1* mutation in our patient. Other genes mapped so far at around the region 6q21 include those for the α-chain of chorionic gonadotropin (*CGA*), α1-chain of type X collagen (*COL10A1*) and for myristoylated alanine-rich protein kinase C substrate (*MARCKS*), and the FYN tyrosine kinase proto-oncogene (*FYN*). Although these genes have not been reported to be a cause of the heterotaxia, they may be related to the expression of other phenotypes in our patient.

Two loci, *Iv* and *Inv*, that contribute to situs abnormalities in the mouse have been identified [Brueckner et al., 1989; Yokoyama et al., 1993]. *Iv* lies on mouse chromosome 12 and is tightly linked to the mouse immunoglobulin heavy chain gene (*Igh*) cluster [Brueckner et al., 1989; Hanzlik et al., 1990]. Chromosomal localization (14q32) of human *IGH* [Nakamura et al., 1989] does not correspond to any of the breakpoints in our patient. The other locus in the mouse, *Inv*, is located to mouse chromosome 4 between the two genes, *Tsha* and *Hxb*, whose human homologs have been assigned to 6q14-q21 and 9q32-q34, respectively [Yokoyama et al., 1993]. Therefore, it is also less likely that the hypothetical human *INV* contributes to the heterotaxia in our patient.

ACKNOWLEDGMENTS

N.N. is supported in part by grants-in-aid for Scientific Research from the Ministry of Education, Science and Culture and from the Ministry of Health and Welfare of Japan.

REFERENCES

Alonso S, Pierpont ME, Radtke W, Martinez J, Chen S-c, Grant JW, Dhnert I, Taviaux S, Romey M-C, Demaille J, Bouvagnet P (1995): Heterotaxia syndrome and autosomal dominant inheritance. Am J Med Genet 56:12–15.

Arnold GL, Bixler D, Girod D (1983): Probable autosomal recessive inheritance of polysplenia, situs inversus and cardiac defects in an Amish family. Am J Med Genet 16:35–42.

Britz-Cunningham SH, Shah MM, Martinez A-M, Fletcher WH (1993): Mutations of the connexin43 (α1) gene are associated with defects in heart development. Mol Biol Cell 4:329a.

Britz-Cunningham SH, Shah MM, Zuppan CW, Fletcher WH (1995): Mutations in the connexin43 gap-junction gene in patients with heart malformations and defects of laterality. N Engl J Med 332:1323–1329.

Brueckner M, D'Eustachio P, Horwich AL (1989): Linkage mapping of a mouse gene, *iv*, that controls left-right asymmetry of the heart and viscera. Proc Natl Acad Sci USA 86:5035–5038.

Casey B, Devoto M, Jones KL, Ballabio A (1993): Mapping a gene for familial situs abnormalities to human chromosome Xq24-q27.1. Nature Genet 5:403–407.

Corcos IA, Meese EU, Loch-Caruso R (1993): Human connexin43 gene locus, *GJA1*, sublocalized to band 6q21-q23.2. Cytogenet Cell Genet 64:31–32.

Czeizel A (1987): Familial situs inversus and congenital heart defects. Am J Med Genet 28:227–228.

Distefano G, Romeo MG, Grasso S, Mazzone D, Sciacca P, Mollica F (1987): Dextrocardia with and without situs viscerum inversus in two sibs. Am J Med Genet 27:929–934.

Fukushima Y, Ohashi H, Wakui K, Fujiwara M, Nakamura Y, Ogawa K (1993): Polysplenia syndrome and paracentric inversion of chromosome 11[46,XX,inv(11)(q13q25)]. Am J Hum Genet 53: 1543A.

Gatrad AR, Read AP, Watson GH (1984): Consanguinity and complex cardiac anomalies with situs ambiguous. Arch Dis Child 59: 242–245.

Hanzlik AJ, Binder M, Layton WM, Rowe L, Layton M, Taylor BA, Osemlak MM, Richards JE, Kurnit DM, Stewart GD (1990): The murine situs inversus viscerum (*iv*) gene responsible for visceral asymmetry is linked tightly to the Igh-C cluster on chromosome 12. Genomics 7:389–393.

Nakamura Y, Lathrop M, O'Connell P, Leppert M, Kamboh MI, Lalouel J-M, White R (1989): Frequent recombination is observed in the distal end of the long arm of chromosome 14. Genomics 4:76–81.

Niikawa N, Kohsaka S, Mizumoto M, Hamada I, Kajii T (1983): Familial clustering of situs inversus totalis, and asplenia and polysplenia syndromes. Am J Med Genet 16:43–47.

Reaume AG, de Sousa PA, Kulkarni S, Langille BL, Zhu D, Davies TC, Juneja SC, Kidder GM, Rossant J (1995): Cardiac malformation in neonatal mice lacking connexin43. Science 267:1831–1834.

Wilson GN, Stout JP, Schneider NR, Zneimer SM, Gilstrap LC (1991): Balanced translocation 12/13 and situs abnormalities: Homology of early pattern formation in man and lower organisms? Am J Med Genet 38:601–607.

Yokoyama T, Copeland NG, Jenkins NA, Montgomery CA, Elder FFB, Overbeek PA (1993): Reversal of left-right asymmetry: A situs inversus mutation. Science 260:679–682.

Zlotogora J, Schimmel MS, Glaser Y (1987): Familial situs inversus and congenital heart defects. Am J Med Genet 26:181–184.